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Total and specific fluid consumption as determinants of bladder cancer risk

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We pooled the data from 6 case-control studies of bladder cancer with detailed information on fluid intake and water pollutants, particularly trihalomethanes (THM), and evaluated the bladder cancer risk associated with total and specific fluid consumption. The analysis included 2,729 cases and 5,150 controls. Odds ratios (OR) and 95% confidence intervals (CI) for fluid consumption were adjusted for age, gender, study, smoking status, occupation and education. Total fluid intake was associated with an increased risk of bladder cancer in men. The adjusted OR for 1 l/day increase in intake was 1.08, (95% CI 1.03–1.14, *p*-value for linear trend <0.001), while no trend was observed in women (OR = 1.04, 0.94–1.15; *p*-value = 0.7). OR was 1.33 (1.12–1.58) for men in the highest category of intake (>3.5 l/day) as compared to those in the lowest (≤2 l/day). An increased risk was associated with intake of tap water. OR for >2 l/day *vs.* ≤0.5 l/day was 1.46 (1.20–1.78), with a higher risk among men (OR = 1.50, 1.21–1.88). No increased risk was observed for the same intake groups of nontap water in men (OR = 0.97, 0.77–1.22) or in women (OR = 0.85, 0.50–1.42). Increased bladder cancer risks were observed for an intake of >5 cups of coffee daily *vs.* <5 and for THM exposure, but neither exposure confounded or modified the OR for tap water intake. The association of bladder cancer with tap water consumption, but not with nontap water fluids, suggests that carcinogenic chemicals in tap water may explain the increased risk.

Key words: bladder cancer; fluid consumption; tap water; pooled analysis; case-control study

Prolonged exposure of the urothelium to carcinogens in the urine may affect the development of bladder cancer. Epidemiological studies have evaluated the risk for bladder cancer in relation to the quantity of fluid intake with controversial results. The strongest evidence of a protective effect of high fluid intake comes from the Health Professionals follow-up study.[1] An increase of total fluid intake by 240 ml decreased the risk by 7%, after adjusting for type of beverages. Subjects consuming >2,531 ml/day of total fluids had a 49% lower risk than those drinking <1,290 ml/day. Other cohort studies have not found a clear evidence of protective nor positive association.[2,3] In contrast, an excess risk in subjects with high total fluid intake has been found by some[4–11] though not all[12–15] case-control studies.

High fluid intake could reduce the contact of carcinogens with the urothelium by diluting the urine or increasing the frequency of urination. By contrast, high fluid intake could increase the risk if it contains contaminants that are bladder carcinogens.[16] The positive associations in some studies may be attributed to the type of fluid, such as coffee or chlorinated drinking water, which may contain carcinogenic agents. Drinking more than 5–10 cups of coffee per day has been related to bladder cancer both in smokers and nonsmokers. However, the evidence is not entirely consistent.[17] Bladder cancer has been consistently associated with exposure to disinfection by-products (DBP) and arsenic in drinking water.[18,19] DBP are chemicals generated through reactions of disinfectants (*e.g.* chlorine), with organic matter naturally occurring in water. Trihalomethanes (THM) are usually the most prevalent by-products of chlorination, followed by haloacetic acids (HAA), and to a lesser extent other chemicals such as haloketones, haloacetonitriles and others.[20] Voiding frequency, which influences the time of urine retention in the bladder, has not been examined in epidemiological studies; however, experimental evidence has associated low voiding frequency with higher formation of DNA adducts to 4-aminobiphenyl, an aromatic amine.[21]

We pooled the primary data from 6 case-control studies of bladder cancer, with detailed information on fluid intake and water pollutants, particularly, THM levels as a marker of DBP mixtures, and evaluated whether total fluid intake and intake of some specific fluids are associated with bladder cancer risk.

Material and methods

Studies

We obtained the primary data from 6 studies that met the following inclusion criteria: (*i*) case-control studies of incident bladder cancer, (*ii*) availability of information on fluid and coffee consumption and detailed long-term exposure assessment to THM and (*iii*) accessibility to primary data. We identified the published studies through Medline searches. Unpublished studies were identified through personal contacts with research groups that had collaborated on previous pooled analyses of bladder cancer.[17,22,23] The pooled database included 2 studies from the United States,[11,24] and 1 each from Canada,[25] Finland,[26] France[27] and Italy,[28] conducted between 1978 and 2000. The results of the effects of fluid intake in the French study have been published.[6] The results of the effects of THM exposure based on this pooled data set have also been published.[18] Detailed information on THM was available for only part of a large US study,[16] and that part was incorporated in the pooled analysis.[24] Data from a second study from the United States[29] were not accessible and were not included in this analysis. The principal investigators of the pooled project and of the individual studies met and discussed the protocol and operational decisions for the analyses.

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TABLE I – CHARACTERISTICS OF CASES AND CONTROLS IN THE POOLED STUDY POPULATION (N = 7,879)

	Cases (%) (N = 2,729)	Controls (%) (N = 5,150)	OR (95% CI)[1]
Study and site			
Porru 2004 (Italy)	25 (1)	37 (1)	
King 1996 (Canada)	679 (25)	1,506 (29)	
Koivusalo 1998 (Finland)	609 (23)	1,054 (20)	
Cantor 1998 (USA)	904 (33)	1,689 (33)	
Cordier 1993 (France)	256 (9)	310 (6)	
Lynch 1989 (USA)	256 (9)	554 (11)	
Sex			
Men	2,126 (78)	3,514 (68)	
Women	603 (22)	1,636 (32)	
Age[2]			
<67 years	1,355 (50)	2,845 (55)	
>67 years	1,374 (50)	2,305 (45)	
Smoking			
Never smoker[3]	539 (20)	2,043 (40)	1.00
Ex-smoker	1,078 (39)	1,853 (36)	2.02 (1.77–2.29)
Current smoker	1,112 (41)	1,254 (24)	3.52 (3.09–4.01)
Worked in high-risk occupations			
Never[3]	1,787 (65)	3,556 (69)	1.00
Ever	492 (18)	665 (13)	1.39 (1.22–1.58)
Unclassifiable	450 (17)	929 (18)	1.09 (0.96–1.24)
Education			
≤Primary school[3]	534 (20)	944 (18)	1.00
Some secondary	818 (30)	1,166 (23)	1.32 (1.14–1.51)
Secondary completed	664 (24)	1,415 (28)	0.93 (0.81–1.08)
>Secondary	558 (20)	1,300 (25)	0.87 (0.75–1.01)
Other	155 (6)	325 (6)	0.86 (0.69–1.08)

[1]OR from logistic regression adjusted for study, sex and age.–[2]Dichotomous at the median.–[3]Reference category.

Data

We extracted from the original databases exposure information and covariates that might be potential confounders or effect modifiers: total fluid, total tap water and coffee consumption, THM exposure, age, sex, smoking status (never smokers; exsmokers, quitting 2 years before the interview; current smokers), ever worked in an *a priori* high-risk occupation[30] and socio-economic status (years of education). Education was categorized into 4 groups: primary school completed or less, some secondary education, secondary education completed and higher education. We established common definitions and coding schemes for all variables. A separate occupational classification had to be used for the Canadian study, and the high-risk occupations are therefore not identical to those used in the remaining 5 studies. We excluded subjects below 30 and above 80 years old (n = 1,149) from the pooled study population, as well as patients with >2 years between diagnosis and interview (n = 166). The final pooled data set comprised 3,419 cases and 6,077 controls. Statistical analyses were done in a subset with complete information for all variables (2,729 cases and 5,150 controls). All cases included in the pooled analysis had histologically confirmed cancers of the bladder. Five studies (Cordier, King, Koivusalo, Porru) included all histologies, and the study by Cantor only included transitional cell carcinomas. Four studies enrolled population controls.[11,24–26] The remaining 2 recruited hospital controls, 1 study using urological controls (Porru) and the second, patients from various wards diagnosed with osteoarticular, digestive and heart diseases (Cordier 1993).[27] Controls were individually or frequency matched to cases for age, sex and geographic area.

Fluid consumption variables

Total fluid consumption included intake of all types of fluids, such as water *per se,* tea, coffee, alcoholic beverages and soft drinks. Total tap water included water *per se* plus water-based preparations, such as coffee and hot tea. Coffee intake included all types of coffee (regular, instant, decaffeinated, *etc*.). Consequently, coffee and tea were included in tap water, and tap water was included in total fluid consumption. We calculated intake of nontap water fluids by subtracting tap water from total fluid consumption. Noncoffee tap water intake was calculated by subtracting coffee from tap water consumption. Data on alcohol consumption were only available in 3 studies and was not included in the analyses. Average residential THM exposure (μg/l) was calculated as the sum of the year-by-year annual municipal mean THM level in each residence, divided by the number of years with nonmissing THM data, during an exposure window of 40 years (from 5 to 45 years before the interview).

The way studies ascertained fluid consumption from participants differed. Participants in the study by Cantor *et al*.[11] were asked to estimate consumptions ''as an adult''. Cordier *et al*.[27] asked about fluid consumption since age 18 and about changes in consumption habits. They then estimated mean consumption of beverages in the period from age 18 until diagnosis. Lynch *et al*.[24] asked respondents to estimate the amount of various beverages they drank ''in the winter 1 year ago'' (to minimize seasonal influences). King *et al*.[25] asked participants about fluid consumption 2 years prior diagnosis. Koivusalo *et al*.[26] asked about fluid consumption in the 1980s. The study by Porru *et al*.[28] asked for lifetime habits and recorded qualitative and quantitative variations for coffee, tea, alcohol and soft drinks.

Statistical analysis

We described the exposure variables by case-control status and evaluated the statistical significance of the differences using a nonparametric test (Mann-Whitney) for continuous variables and χ^2 test for categorical variables. We used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CI) for the different exposure indices. All ORs were adjusted by study, age (continuous), sex (when not stratified), socio-economic status (education), smoking status (never, ex- and current smokers), and ever worked in an *a priori* high-risk occupation.[30] Further adjustment for pack-years of smoking did not mod-

TABLE II – FLUID CONSUMPTION AND THM EXPOSURE IN THE STUDY POPULATION

	Men			Women		
	Cases	Controls	*p*-value[1]	Cases	Controls	*p*-value[1]
Total fluid consumption (l/day)						
Mean (SD)	2.7 (1.2)	2.6 (1.1)	0.001	2.6 (1.1)	2.6 (1.0)	0.665
Range	0.3–10.3	0.1–10.9		0.5–10.9	0.4–8.0	
Median	2.6	2.5		2.5	2.5	
Tap water consumption (l/day)						
Mean (SD)	1.6 (1.2)	1.5 (1.1)	0.006	1.7 (1.1)	1.7 (1.0)	0.219
Range	0–9.0	0–10.6		0–10.4	0–7.5	
Median	1.5	1.5		1.6	1.7	
Coffee intake (l/day)						
Mean (SD)	0.6 (0.5)	0.5 (0.5)	0.044	0.6 (0.5)	0.5 (0.5)	0.137
Range	0–5.7	0–5.7		0–3.3	0–6.0	
Median	0.5	0.5		0.4	0.4	
Coffee intake (cups/day)						
0–5	1727 (81%)	2985 (85%)		495 (82%)	1431 (87%)	
>5	399 (19%)	529 (15%)	<0.001	108 (18%)	205 (13%)	0.001
Noncoffee tap water consumption (l/day)						
Mean (SD)	1.1 (0.9)	1.1 (0.9)	0.167	1.2 (1.0)	1.2 (0.9)	0.065
Range	0–7.0	0–10.4		0–10.1	0–5.7	
Median	1.0	0.9		1.1	1.2	
Nontap water fluids (l/day)						
Mean (SD)	1.1 (0.8)	1.1 (0.8)	0.289	0.9 (0.6)	0.9 (0.6)	0.342
Range	0–6.4	0–6.0		0–3.9	0–5.9	
Median	1.0	1.0		0.8	0.7	
Average residential THM exposure (μg/l)						
Mean (SD)	20.0 (25.0)	17.4 (23.4)	<0.001	21.1 (25.9)	21.0 (24.8)	0.659
Range	0–130.0	0–124.7		0–128.2	0–130.0	
Median	5.0	3.0		9.7	7.3	

[1]Mann-Whitney test for continuous and χ^2test for categorical variables.

ify risk estimates and are not reported. Total fluid, tap water, coffee and nontap water fluid intake were initially treated as continuous variables in litres per day. To examine the exposure-response relation, subjects were grouped using the same boundaries for different fluids. Coffee intake was grouped into 2 categories: ≤5, and >5 cups of coffee per day. THM exposure was treated as categorical, grouped by quartiles among controls. Analyses were limited to 7,879 subjects (2,729 cases and 5,150 controls). This study population comprised subjects with no missing data for any of the included variables, and whose THM exposure was known for at least 70% of the exposure window. The proportions of controls and women were higher in the included (65% controls and 28% women) compared to the excluded population (57% controls and 19% women). Median age was slightly lower in the included (64 *vs.* 65 years among the excluded). Risk of bladder cancer for smoking status was similar in both groups. To check for potential effect modification by smoking and THM exposure, we stratified the analyses and calculated the OR of bladder cancer for the different fluid variables among never and current smokers, as well as among subjects with low and medium–high exposure to THM (cut-off defined by the median, 5 μg/l). Adjusted ORs were calculated for different types of fluid consumption within individual studies, and the heterogeneity of effects among studies was evaluated through a meta-analysis.[31] Analyses were performed using the statistical package STATA v.8.0.

Results

A total of 78% of cases and 68% of controls in the study population were men. The median age at interview was 67 years. After adjusting for study, sex and age, excess risks were found for ex- and current smokers and those who had ever worked in an *a priori* high-risk occupation (Table I). ORs for smoking status and education were similar for men and women. For occupation, ORs were higher among men.

Total fluid consumption in the overall study population was on average 2.66 l/day (2.71 among cases and 2.63 among controls). Average tap water ingestion was 1.60 l/day (1.63 among cases and 1.59 in controls). Nontap water fluid intake was on average 1.05 l/day (1.08 in cases and 1.04 in controls). Daily coffee intake was 0.56 l/day (0.58 in cases and 0.54 in controls), on average, 16% of the study subjects drank >5 cups of coffee per day (19% among cases and 14% among controls). Noncoffee tap water intake was 1.11 l/day among cases and controls. Data on alcohol consumption were available for 3 of the studies, showing a wide variation. Among controls, alcohol consumption (including wine, beer and liquors) from total fluid consumption was 40.6% among men and 14.4% among women in the French study,[27] 29% in the Italian study (which included only men)[28] and 7.7% (men) and 1.8% (women) in the study by Lynch *et al.*[24] Average residential THM exposure was 19.1 μg/l (20.3 in cases and 18.6 in controls) (Table II).

After adjusting for potential confounders, total fluid intake was associated with an increased risk of bladder cancer, with an OR of 1.08 (95% CI = 1.03–1.13) per litre increase in daily total fluid consumption (overall for men and women). Risks were higher in men (OR = 1.08) than in women (OR = 1.04), and this difference by sex was statistically significant (*p*-value for the interaction term between sex and total fluid consumption—split in the median—was 0.018). A dose-response pattern was found, with the OR overall (men and women) of 1.26 (95% CI = 1.08–1.47) for the highest category of total fluid consumption (>3.5 l/day) compared to the lowest category (≤2.0 l/day); *p*-value for linear trend was <0.001. This trend was statistically significant only in men (Table III).

Tap water consumption was associated with an increased risk of bladder cancer. The adjusted OR/l/day increase overall was 1.10, 95% CI = 1.04–1.17 with higher ORs observed in men than in women. The OR for the highest category of intake (>2.0 l/day) relative to the lowest (≤0.5 l/day) was 1.46 (95% CI = 1.20–1.78, *p*-value for linear trend <0.001). After excluding coffee from the total tap water consumption, OR still showed an association among men, OR = 1.09 (95% CI = 1.01–1.18) with a slightly

TABLE III – ODDS RATIO (OR) AND 95% CONFIDENCE INTERVALS (CI) OF BLADDER CANCER BY AMOUNT AND TYPE OF FLUID CONSUMPTION ADJUSTED FOR AGE, STUDY, EDUCATION, SMOKING STATUS AND EVER WORKED IN A HIGH-RISK OCCUPATION

	Men		Women	
	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls
Total fluid (l/day)				
Continuous	1.08 (1.03–1.14)		1.04 (0.94–1.15)	
≤2.0	1.00	607/1,132	1.00	198/500
>2.0–2.5	1.18 (1.00–1.39)	434/717	0.93 (0.70–1.23)	123/375
>2.5–3.0	1.12 (0.94–1.34)	339/599	1.11 (0.83–1.49)	115/297
>3.0–3.5	1.39 (1.15–1.69)	306/433	0.94 (0.68–1.31)	77/219
>3.5	1.33 (1.12–1.58)	440/633	1.06 (0.77–1.46)	90/245
p-trend	<0.001		0.702	
Tap water (l/day)				
Continuous	1.12 (1.05–1.19)		1.04 (0.93–1.17)	
≤0.5	1.00	398/718	1.00	81/180
>0.5–1.0	1.20 (0.99–1.46)	352/554	1.03 (0.71–1.51)	97/245
>1.0–1.5	1.16 (0.94–1.45)	301/564	1.07 (0.71–1.62)	93/273
>1.5–2.0	1.24 (0.99–1.55)	374/665	1.14 (0.75–1.72)	119/355
>2.0	1.50 (1.21–1.88)	701/1,013	1.19 (0.78–1.81)	213/583
p-trend	<0.001		0.340	
Coffee				
Continuous (l/d)	1.11 (0.98–1.25)		0.93 (0.75–1.15)	
≤5 cups/day	1.00	1,727/2,985	1.00	495/1,431
>5 cups/day	1.23 (1.05–1.44)	399/529	1.31 (0.99–1.74)	108/205
Noncoffee tap water fluids (l/day)				
Continuous	1.09 (1.01–1.18)		1.06 (0.93–1.20)	
≤0.5	1.00	690/1,189	1.00	165/377
>0.5–1.0	1.19 (0.99–1.42)	413/659	0.95 (0.68–1.32)	103/298
>1.0–1.5	1.08 (0.89–1.31)	374/692	1.14 (0.81–1.61)	126/364
>1.5–2.0	1.35 (1.09–1.67)	320/488	1.24 (0.86–1.79)	114/301
>2.0	1.36 (1.10–1.69)	329/486	1.07 (0.74–1.56)	95/296
p-trend	0.004		0.381	
Non-tap water fluids (l/day)				
Continuous	1.03 (0.95–1.12)		1.03 (0.85–1.24)	
≤0.5	1.00	579/936	1.00	227/590
>0.5–1.0	0.93 (0.78–1.10)	512/921	0.90 (0.68–1.20)	150/487
>1.0–1.5	1.10 (0.91–1.33)	488/775	1.03 (0.74–1.42)	131/339
>1.5–2.0	1.07 (0.86–1.33)	297/451	1.17 (0.78–1.75)	64/142
>2.0	0.97 (0.77–1.22)	250/431	0.85 (0.50–1.42)	31/78
p-trend	0.693		0.817	

lower risk observed in women (OR = 1.06, 0.93–1.20). Similar to total tap water intake, the dose-response trend was statistically significant in men (*p*-trend = 0.004) and not in women, (*p*-trend = 0.38) (Table III). *p*-value for the interaction between sex and tap water (split by the median) was <0.001.

OR for nontap water fluids intake was overall 1.03 (95% CI = 0.96–1.10) per litre increase in daily consumption. The OR for the highest category of nontap water fluids ingestion (>2.0 l/day) compared to the lowest quartile (≤0.5 l/day) was 0.95 (95% CI = 0.78–1.17), and *p* value for linear trend = 0.65. There was no evidence of interaction with sex; *p*-value for the interaction term was 0.137 (Table III).

The OR per litre increase in daily coffee consumption was 1.08 (95% CI = 0.97–1.20) overall men and women. Consuming >5 cups of coffee per day was associated with an overall OR of 1.26, 95% CI = 1.10–1.44, compared to those who consumed less or equal to 5 cups of coffee per day. These associations remained after additional adjustment for total nontap water fluid consumption. Among men, the OR was 1.23 (95% CI = 1.05–1.44) and among women, 1.31 (95% CI = 0.99–1.74) (Table III). For those 5 studies with available data on pack-years, the OR for drinking >5 cups of coffee per day relative to 0–5 cups/day for both sexes combined was 1.25 (1.08–1.44) adjusting for smoking status and 1.24 (1.08–1.43) adjusting for quartiles of pack-years. *p*-value for the interaction term between sex and coffee consumption (0–5 *vs.* >5 cups/day) was 0.790.

Average residential THM level was associated with an increased risk of bladder cancer with a dose-response pattern. However, we did not find evidence that THM exposure confounded or modified the risk associated with tap water intake. For the highest quartile of THM exposure (>35.0 μg/l), the OR among men was 1.50 (95% CI = 1.27–1.78), relative to the lowest quartile of THM exposure (≤0.5 μg/l). The *p*-value for linear trend was <0.001. Among women, the OR was 0.90 (95% CI = 0.67–1.21), *p*-trend = 0.50. Risk estimates among men for the combined effects of tap water consumption and average residential THM level are shown in Table IV. Risk of bladder cancer increased for tap water consumption and for average residential THM exposure in men. No associations were found in women for THM exposure or the combined risk estimates tap water-THM levels. Among women with high tap water consumption (>2.22 l/day) and high THM exposure (>35.0 μg/l), the OR was 0.86 (0.48–1.54) compared with those with low tap water consumption (≤0.8 l/day) and low THM exposure (≤0.5 μg/l). The ORs for risk of bladder cancer with total fluid consumption or its components (tap water, nontap water fluids, coffee and noncoffee total tap water), adjusting additionally for quartiles of average residential THM, were essentially unaffected. The risk of bladder cancer with fluid consumption or its components was similar among men with low exposure to THM (≤5 μg/l) compared to men with moderate exposure (>5 μg/l). The OR remained similar for men exposed to higher THM levels (>30 μg/l).

Adjusting for smoking status reduced the OR of bladder cancer for total fluid consumption (and its components) compared to the unadjusted risk estimates. For total fluids, the unadjusted OR among men per litre/day increase was 1.12 (95% CI = 1.06–1.18); for tap water, 1.14 (95% CI = 1.07–1.21); for nontap water fluids, 1.08 (95% CI = 0.99–1.17); for coffee, 1.32 (95% CI =

TABLE IV – ODDS RATIOS (95% CI) AMONG MEN BY COMBINED EFFECTS OF TAP WATER CONSUMPTION AND AVERAGE RESIDENTIAL THM EXPOSURE ADJUSTED FOR AGE, STUDY, EDUCATION, SMOKING STATUS AND EVER WORKED IN A HIGH-RISK OCCUPATION

Average residential THM level (μg/l)	Tap water intake (l/day)				Overall
	≤0.80	>0.80–1.54	>1.54–2.22	>2.22	
≤0.5	1.00 [206, 466]	1.40 (1.03–1.90) [110, 199]	1.26 (0.92–1.74) [100, 214]	1.50 (1.08–2.09) [106, 204]	1.00 [522, 1083]
>0.5–5.0	1.32 (0.99–1.76) [152, 259]	1.48 (1.07–2.06) [98, 171]	2.07 (1.49–2.88) [131, 176]	1.76 (1.28–2.41) [174, 250]	1.29 (1.09–1.53) [555, 856]
>5.0–35.0	1.60 (1.15–2.22) [90, 139]	1.32 (0.95–1.83) [95, 215]	1.90 (1.37–2.64) [119, 186]	2.10 (1.52–2.88) [154, 209]	1.38 (1.16–1.64) [458, 749]
>35.0	1.85 (1.40–2.45) [176, 197]	1.71 (1.27–2.31) [140, 226]	1.68 (1.23–2.30) [145, 239]	2.20 (1.58–3.08) [130, 164]	1.50 (1.27–1.78) [591, 826]
Overall	1.00 [624, 1061]	1.10 (0.92–1.31) [443, 811]	1.25 (1.02–1.52) [495, 815]	1.37 (1.11–1.69) [564, 827]	

Numbers of cases and controls in each group are shown in brackets.

1.18–1.49) and for noncoffee tap water consumption, 1.05 (95% CI = 0.98–1.13). Adjusted ORs shown in Table III are similar to the ORs among never-smoking men (except for heavy coffee consumption), showing no evidence of residual confounding by smoking. The ORs for total fluid and its components (except coffee) were similar among never- and ever smokers, showing no or weak evidence of effect modification for smoking. However, the OR for being a heavy coffee drinker (>5 cups of coffee per day) was higher among ever smokers (OR = 1.36, 95% CI = 1.15–1.60 for men and 1.33, 0.94–1.88 for women) compared to never smokers, where the association was close to the null (OR = 1.13, 95% CI = 0.69–1.84 among men and 1.28, 0.77–2.13 among women). Nevertheless, *p*-value for the interaction term between coffee consumption and smoking status was nonsignificant (0.406 for men and 0.562 for women).

A consistently small increase in risk of bladder cancer with total fluid consumption (Fig. 1*a*) and tap water intake in men (Fig. 1*b*) was found in each study, individually. For nontap water fluid intake, OR did not follow a consistent pattern among studies (Fig. 1*c*). Meta-analysis of the adjusted study-specific risk estimates revealed no significant heterogeneity of effects for total fluid intake (*p*-value of heterogeneity was 0.772 for men and 0.769 for women), tap water intake (*p*-value of heterogeneity was 0.616 for men and 0.727 for women) or nontap water fluids (*p*-value of heterogeneity was 0.459 for men and 0.283 for women).

Discussion

We identified an increased risk of bladder cancer for drinking tap-water-based fluids that constituted, on average, two thirds of total fluid consumption. This increase appeared particularly among men. The increased risk for tap water consumption was consistently found in all 6 studies, making chance an unlikely explanation of our results. Men who drank >2.0 l of tap water per day were at almost 50% more risk than those drinking 0.5 l or less. Results among women were less consistent. Coffee constituted on average about one third of the total tap water ingestion. Heavy coffee consumption (>5 cups/day) increased bladder cancer risk, particularly, among ever smokers. Consumption of tap water excluding coffee was also associated with an increased risk of bladder cancer. Consuming fluids other than tap water was not associated with an increased or decreased risk.

We found different risks among men compared to women in total fluid consumption and some of its components. Given the large numbers in this analysis, this difference cannot be attributed solely to chance due to small numbers among women. This differential risk by sex has been found in most of the case-control studies reporting results stratified by gender, without a homogeneous pattern. For total fluid intake, some studies found an increased risk among men and a lower, null or decreased risk among women;[4,6,8] an increased risk among women, but a null association among men, is reported in other studies;[9,10] some studies found a protective effect among women, and an association close to the null among men;[13,15] and finally, similar risks in men and women are found in other studies.[7,11] A large cohort study[1] examined risk only among men. A different consumption pattern between men and women of certain fluids is not a likely explanation for the sex difference we observed. We examined many types of fluids and found similar differences by sex. We were not able to do specific analyses for alcohol consumption, since this information was only available for 3 studies. However, the association between alcohol consumption and bladder cancer risk is not well established, with most of literature reporting nonsignificant or no association.[6,32–34] Consequently, alcohol consumption is not likely to bias or confound our results. It has been previously observed that even in the absence of smoking and occupational exposures, an increased risk was found in men compared to women,[35] which could be attributed to differences in environmental and dietary exposures not yet identified or innate sexual characteristics such as anatomic differences, urination habits or hormonal factors. In short, findings by gender are difficult to explain under scenarios of causal relationship or biases with which we are familiar.

Our results were consistent with those from case-control studies that found a positive association with total fluid or tap water consumption.[4,5,7–10] The discrepancy with studies that observed a protective effect, such as the Health Professionals follow-up study,[1] could be explained by differences in the characteristics of the study population, differences in the components of the total fluid variable and different carcinogens in the tap water or other fluids.

The association with tap water consumption, but not with nontap water fluids, suggests that the increased risk for tap water may be related to the presence of carcinogens such as other DBP in the tap water. THM, although associated with an increased risk of bladder cancer, did not confound the results nor modify the main effects of the different types of fluid consumption. DBP are a complex mixture of chemicals, and about 50% of total organic halides (TOX) are unidentified compounds.[36] Consequently, THM do not necessarily reflect the levels of other DBP that could play a role in the carcinogenesis of bladder cancer.[37] The chemistry of DBP is complex, and reactions leading to the formation[38] or removal[39–41] of DBP can occur in the preparation of hot tap-water-based beverages. Thus, THM level in tap water may not reflect ingested levels. In addition to DBP, tap water can contain chemicals that have been described as risk factors for bladder cancer, such as arsenic,[42] and probably many others that have not been identified or evaluated in relation to bladder cancer, but that could have some carcinogenic potential (metals, radioisotopes, drug residues, microcystines,[43] *etc*.). Finally, we cannot exclude the combination of several chemicals as a putative risk factor.

To the extent possible, we used common definitions to make variables comparable among studies; however, differences remained. The continuous coffee consumption variable was probably the fluid variable least comparable among studies. In most of the pooled studies, coffee consumption was recorded as

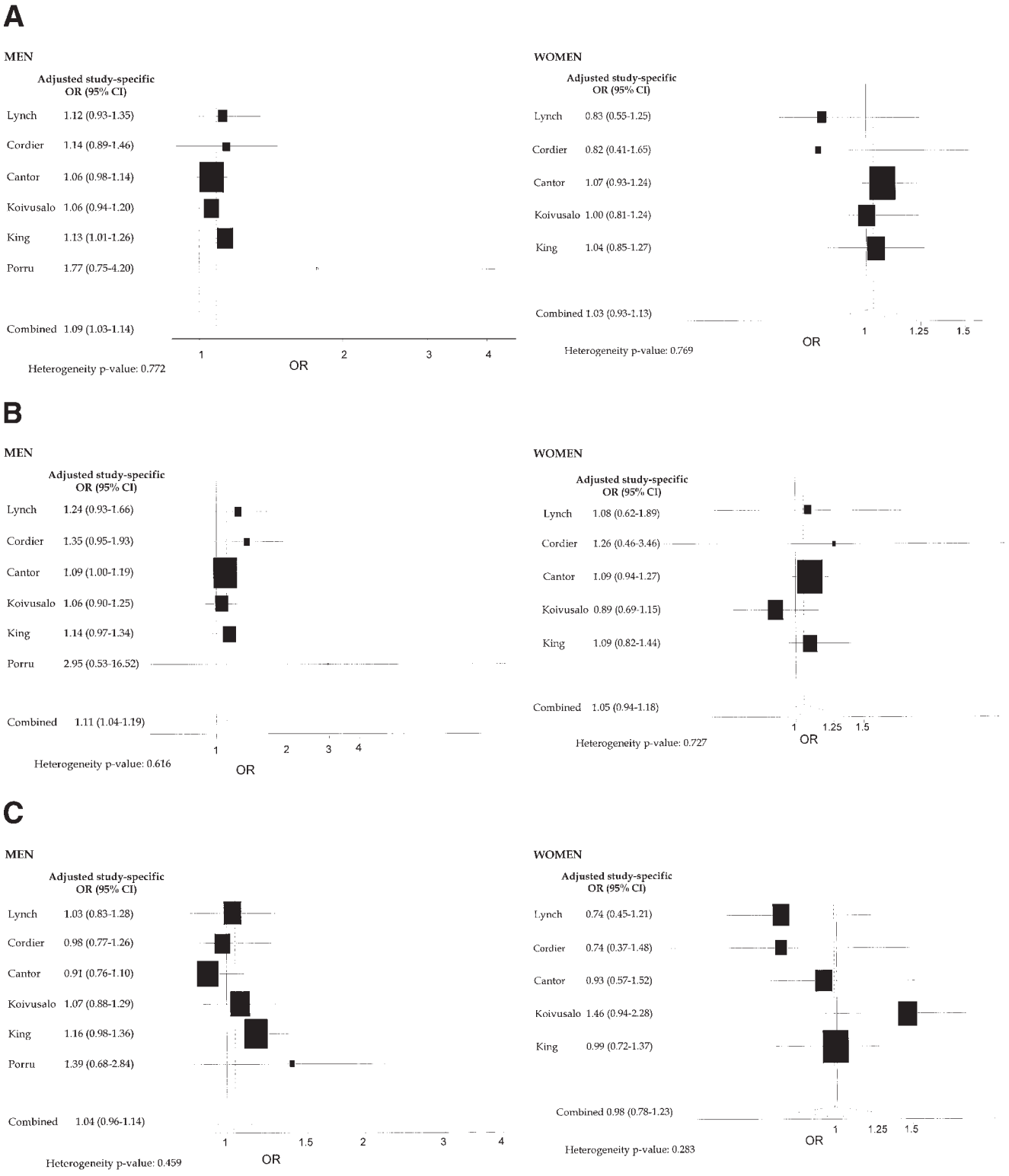

FIGURE 1 – Meta analysis of study-specific odds ratios (OR) adjusted for age, smoking status, education and having ever worked in a high-risk occupation, for different water fluid variables.(*a*) Total fluid consumption (continuous, l/day), (*b*) Tap water intake (continuous, l/day) and (*c*) Nontap water fluids consumption (continuous, l/day).

cups per day. To transform it into litres per day we applied country-specific algorithms (1 cup= 200 ml in North America and Finland and 50 ml in other European studies), reflecting habits by country. This was a simplification that probably led to non-differential misclassification in the continuous coffee variable. In addition, the study by King *et al*. recorded cups of coffee as <1, 1, 2, 3, 4 and 5 or more per day. This more likely introduced misclassification among the highly exposed. Although there was

no heterogeneity of effects in other fluid variables, some measurement error could be present. It is difficult to evaluate quantitatively these errors, although they could be expected to be nondifferential.

Previous studies have examined fluid consumption and use of chlorinated surface water simultaneously.[16] However, this is the first study to evaluate risk of total fluid intake and specific water pollutants (THM) that have previously shown to be associated with bladder cancer risk. We were able to evaluate them independently and to check for confounding and effect modification. Similarly, we could discriminate among different types of fluids. The analysis by specific type of fluid, controlling for THM, is an improvement over previous studies evaluating bladder cancer risk in relation to fluid consumption. Our results provide new evidence and strengthen the framework for hypotheses of possible mechanisms of action. The large study population involving 5 countries represents a major strength of our analysis. Also, being a collaborative study among different research groups has allowed the exchange of knowledge and expertise.

The assessment of the association between fluid consumption and bladder cancer risk is not trivial. Most of the fluids we consume are water-based, and water is a universal solvent that can contain a great number of chemicals (not necessarily toxic). It is difficult to isolate the effect of the fluid itself from the effect of those chemicals. Perhaps the heterogeneous composition of different drinking waters can explain the apparently inconsistent results in epidemiological studies.[1–15]

The public health implications are not clear. Evidence is not yet sufficient to recommend a reduction or an increase in the consumption of certain fluids. We found that drinking tap water was associated with a slight increased risk of bladder cancer, while nontap water fluids were unrelated to bladder cancer risk. This new evidence does not readily translate into public health recommendations. Changing from tap to nontap water (for example, bottled water) systematically could be feasible for some people, but not others. In addition, ''tap water'' or ''total fluid'' is an unspecific term that includes waters with very different qualities. In any event, one implication of our study is that water distributed to the population should be of the highest quality feasible.

In this pooled analysis of 6 case-control studies and almost 8,000 study subjects, we found that tap water ingestion was associated with a slightly increased risk of bladder cancer among men, with a dose-response pattern and independent of THM exposure. Consumption of fluids other than tap water was unrelated to bladder cancer risk. Heavy coffee consumption (>5 cups per day) was associated with an increased risk of bladder cancer among men who smoked. Future studies should explore levels of carcinogens in water and/or other fluids, and voiding frequency since the latter could mitigate the effects of the former. Furthermore, future research should explore the biological mechanisms through which total and specific fluid intake could modify bladder cancer risk. In summary, our results strengthen the hypothesis that fluids by themselves are unrelated to an increased risk of bladder cancer, but that carcinogenic chemicals in fluids could explain the observed increased risks.

References

1. Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Curhan GC, Willett WC, Giovannucci EL. Fluid intake and the risk of bladder cancer in men. N Engl J Med 1999;340:1390–7.
2. Zeegers MPA, Dorant E, Goldbohm RA, van den Brandt PA. Are coffee, tea, and total fluid consumption associated with bladder cancer risk? Results from the Netherlands Cohort Study. Cancer Causes Control 2001;12:231–8.
3. Mills PK, Beeson WL, Phillips RL, Fraser GE. Bladder cancer in a low risk population: results from the Adventist Health Study. Am J Epidemiol 1991;133:230–9.
4. Jensen OM, Wahrendorf J, Knudsen JB, Sorensen BL. The Copenhagen case-control study of bladder cancer. II. Effect of coffee and other beverages. Int J Cancer 1986;37:651–7.
5. Vena JE, Graham S, Freudenheim J, Marshall J, Zielezny M, Swanson M, Sufrin G. Drinking water, fluid intake, and bladder cancer in western New York. Arch Environ Health 1993;48:191–8.
6. Geoffroy-Perez B, Cordier S. Fluid consumption and the risk of bladder cancer: results of a multicenter case-control study. Int J Cancer 2001;93:880–7.
7. Claude J, Kunze E, Frentzel-Beyme R, Paczkowski K, Schneider J, Schubert H. Life-style and occupational risk factors in cancer of the lower urinary tract. Am J Epidemiol 1986;124:578–89.
8. Kunze E, Chang-Claude J, Frentzel-Beyme R. Life style and occupational risk factors for bladder cancer in Germany. A case-control study. Cancer 1992;69:1776–90.
9. Bruemmer B, White E, Vaughan TL, Cheney CL. Fluid intake and the incidence of bladder cancer among middle-aged men and women in a three-county area of western Washington. Nutr Cancer 1997;29: 163–8.
10. Risch HA, Burch JD, Miller AB, Hill GB, Steele R, Howe GR. Dietary factors and the incidence of cancer of the urinary bladder. Am J Epidemiol 1988;127:1179–91.
11. Cantor KP, Lynch CF, Hildesheim ME, Dosemeci M, Lubin J, Alavanja M, Craun G. Drinking water source and chlorination byproducts. I. Risk of bladder cancer. Epidemiology 1998;9:21–8.
12. Slattery ML, West DW, Robison LM. Fluid intake and bladder cancer in Utah. Int J Cancer 1988;42:17–22.
13. Wilkens LR, Kadir MM, Kolonel LN, Nomura AM, Hankin JH. Risk factors for lower urinary tract cancer: the role of total fluid consumption, nitrites and nitrosamines, and selected foods. Cancer Epidemiol Biomarkers Prev 1996;5:161–6.
14. Radosavljevic V, Jankovic S, Marinkovic J, Djokic M. Fluid intake and bladder cancer. A case control study. Neoplasma 2003;50:234–8.
15. Pohlabeln H, Jockel KH, Bolm-Audorff U. Non-occupational risk factors for cancer of the lower urinary tract in Germany. Eur J Epidemiol 1999;15:411–9.
16. Cantor KP, Hoover R, Hartge P, Mason TJ, Silverman DT, Altman R, Austin DF, Child MA, Key CR, Marrett LD, et al. Bladder cancer, drinking water source, and tap water consumption: a case-control study. J Natl Cancer Inst 1987;79:1269–79.
17. Sala M, Cordier S, Chang-Claude J, Donato F, Escolar-Pujolar A, Fernandez F, Gonzalez CA, Greiser E, Jockel KH, Lynge E, Mannetje A, Pohlabeln H, et al. Coffee consumption and bladder cancer in nonsmokers: a pooled analysis of case-control studies in European countries. Cancer Causes Control 2000;11:925–31.
18. Villanueva CM, Cantor KP, Cordier S, Jaakkola JJ, King WD, Lynch CF, Porru S, Kogevinas M. Disinfection byproducts and bladder cancer. A pooled analysis. Epidemiology 2004;15:357–67.
19. Morales KH, Ryan L, Kuo TL, Wu MM, Chen CJ. Risk of internal cancers from arsenic in drinking water. Environ Health Perspect 2000;108:655–61.
20. Shin D, Chung Y, Choi Y, Kim J, Park Y, Kum H. Assessment of disinfection by-products in drinking water in Korea. J Expo Anal Environ Epidemiol 1999;9:192–9.
21. Kadlubar FF, Dooley KL, Teitel CH, Roberts DW, Benson RW, Butler MA, Bailey JR, Young JF, Skipper PW, Tannenbaum SR. Frequency of urination and its effects on metabolism, pharmacokinetics, blood hemoglobin adduct formation, and liver and urinary bladder DNA adduct levels in beagle dogs given the carcinogen 4-aminobiphenyl. Cancer Res 1991;51:4371–7.
22. Mannetje A, Kogevinas M, Chang-Claude J, Cordier S, Gonzalez CA, Hours M, Jockel KH, Bolm-Audorff U, Lynge E, Porru S, Donato F, Ranft U, et al. Smoking as a confounder in case-control studies of occupational bladder cancer in women. Am J Ind Med 1999;36:75–82.
23. Mannetje A, Kogevinas M, Chang-Claude J, Cordier S, Gonzalez CA, Hours M, Jockel KH, Bolm-Audorff U, Lynge E, Porru S, Donato F, Ranft U, et al. Occupation and bladder cancer in European women. Cancer Causes Control 1999;10:209–17.
24. Lynch CF, Woolson RF, O'Gorman T, Cantor KP. Chlorinated drinking water and bladder cancer: effect of misclassification on risk estimates. Arch Environ Health 1989;44:252–9.
25. King WD, Marrett LD. Case-control study of bladder cancer and chlorination by- products in treated water (Ontario, Canada). Cancer Causes Control 1996;7:596–604.
26. Koivusalo M, Hakulinen T, Vartiainen T, Pukkala E, Jaakkola JJ, Tuomisto J. Drinking water mutagenicity and urinary tract cancers: a population-based case-control study in Finland. Am J Epidemiol 1998;148:704–12.
27. Cordier S, Clavel J, Limasset JC, Boccon-Gibod L, Le Moual N, Mandereau L, Hemon D. Occupational risks of bladder cancer in France: a multicentre case- control study. Int J Epidemiol 1993;22: 403–11.

28. Hung RJ, Boffetta P, Brennan P, Malaveille C, Hautefeuille A, Donato F, Gelatti U, Spaliviero M, Placidi D, Carta A, Scotto di Carlo A, Porru S. GST, NAT, SULT1A1, CYP1B1 genetic polymorphisms, interactions with environmental exposures and bladder cancer risk in a high-risk population. Int J Cancer 2005;110:598–604.
29. McGeehin MA, Reif JS, Becher JC, Mangione EJ. Case-control study of bladder cancer and water disinfection methods in Colorado. Am J Epidemiol 1993;138:492–501.
30. Kogevinas M, Trichopoulos D. Urinary bladder cancer. In: Adami HO, Hunter D, Trichopoulos D, eds. Textbook of cancer epidemiology. New York: Oxford University Press, 2002.446–66.
31. DerSimonian R, Laird NM. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
32. Djousse L, Schatzkin A, Chibnik LB, D'Agostino RB, Kreger BE, Ellison RC. Alcohol consumption and the risk of bladder cancer in the Framingham Heart Study. J Natl Cancer Inst 2004;96:1397–400.
33. Pelucchi C, Negri E, Franceschi S, Talamini R, La Vecchia C. Alcohol drinking and bladder cancer. J Clin Epidemiol 2002;55:637–41.
34. Donato F, Boffetta P, Fazioli R, Aulenti V, Gelatti U, Porru S. Bladder cancer, tobacco smoking, coffee and alcohol drinking in Brescia, northern Italy. Eur J Epidemiol 1997;13:795–800.
35. Hartge P, Harvey EB, Linehan WM, Silverman DT, Sullivan JW, Hoover RN, Fraumeni JF, Jr. Unexplained excess risk of bladder cancer in men. J Natl Cancer Inst 1990;82:1636–40.
36. Richardson SD, Simmons JE, Rice G. Disinfection byproducts: the next generation. Environ Sci Technol 2002;36:198A–205A.
37. King WD, Dodds L, Armson BA, Allen AC, Fell DB, Nimrod C. Exposure assessment in epidemiologic studies of adverse pregnancy outcomes and disinfection byproducts. J Expo Anal Environ Epidemiol 2004;14:466–72.
38. Wu WW, Chadik PA, Davis WM, Powell DH, Delfino JJ. Disinfection byproduct formation from the preparation of instant tea. J Agric Food Chem 1998;46:3272–9.
39. Batterman S, Huang AT, Wang S, Zhang L. Reduction of ingestion exposure to trihalomethanes due to volatilization. Environ Sci Technol 2000;34:4418–24.
40. Wu WW, Benjamin MM, Korshin GV. Effects of thermal treatment on halogenated disinfection by-products in drinking water. Water Res 2001;35:3545–50.
41. Li XZ, Sun JM. Further formation of trihalomethanes in drinking water during heating. Int J Environ Health Res 2001;11:343–8.
42. Karagas MR, Tosteson TD, Morris JS, Demidenko E, Mott LA, Heaney J, Schned A. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in new hampshire. Cancer Causes Control 2004;15:465–72.
43. De Figueiredo DR, Azeiteiro UM, Esteves SM, Gonçalves FJ, Pereira MJ. Microcystin-producing blooms—a serious global public health issue. Ecotoxicol Environ Saf 2004;59:151–63.